

New Concepts in Cervical Screening

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Outline

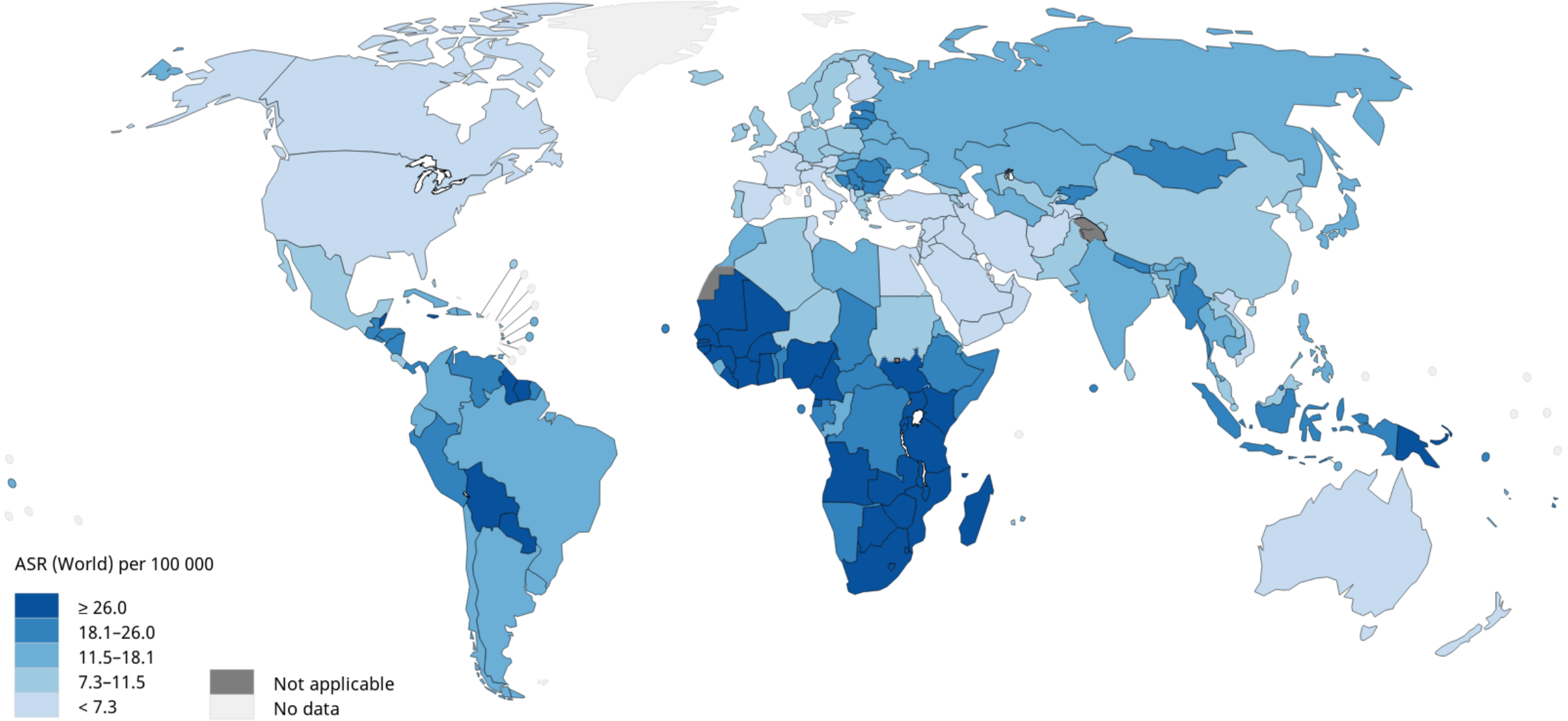
Cervical Cancer Epidemiology

Cervical screening – The Past

Cervical screening – The Present

Cervical screening – The Future

Estimated age-standardized incidence rates (World) in 2018, cervix uteri, all ages



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Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

http://gco.iarc.fr

World Health Organization

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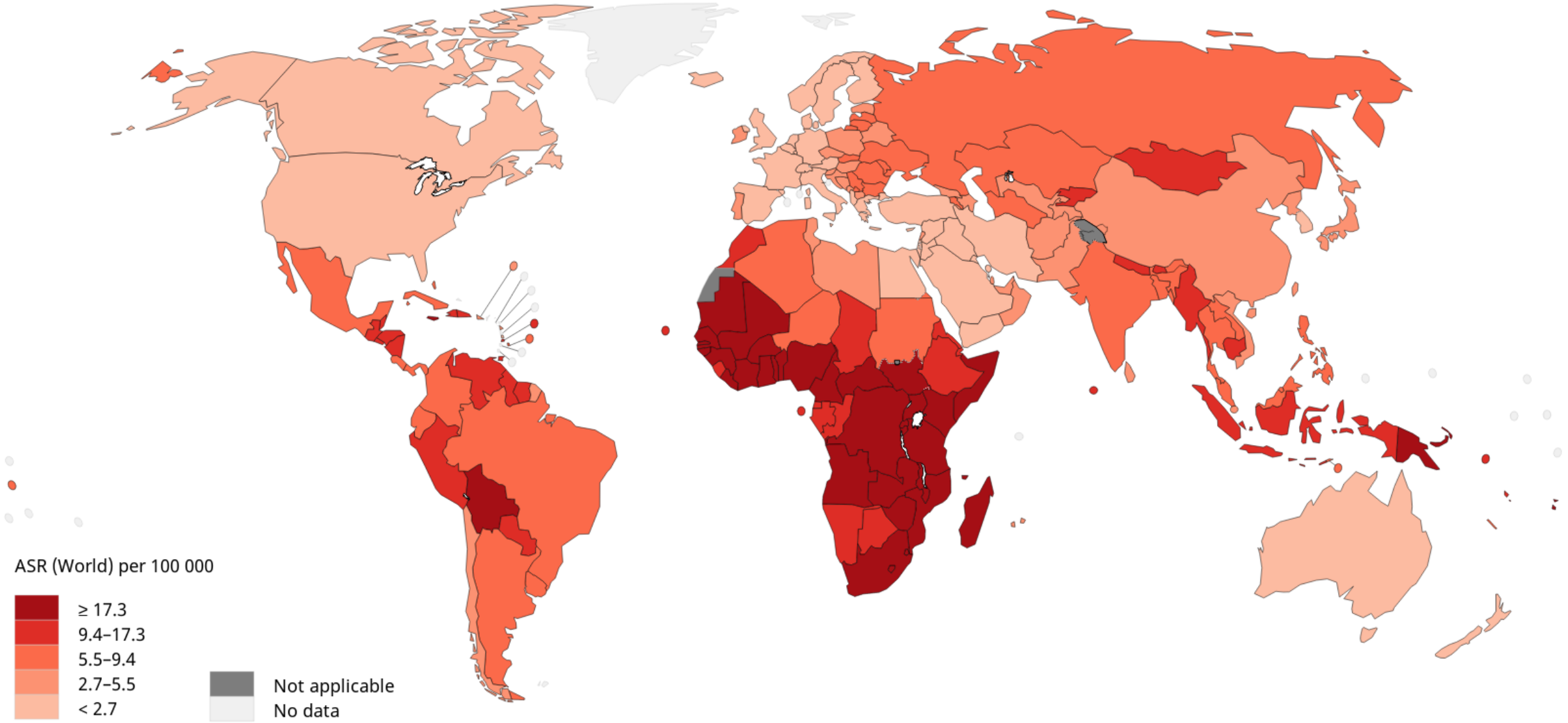
Estimated age-standardized mortality rates (World) in 2018, cervix uteri, all ages



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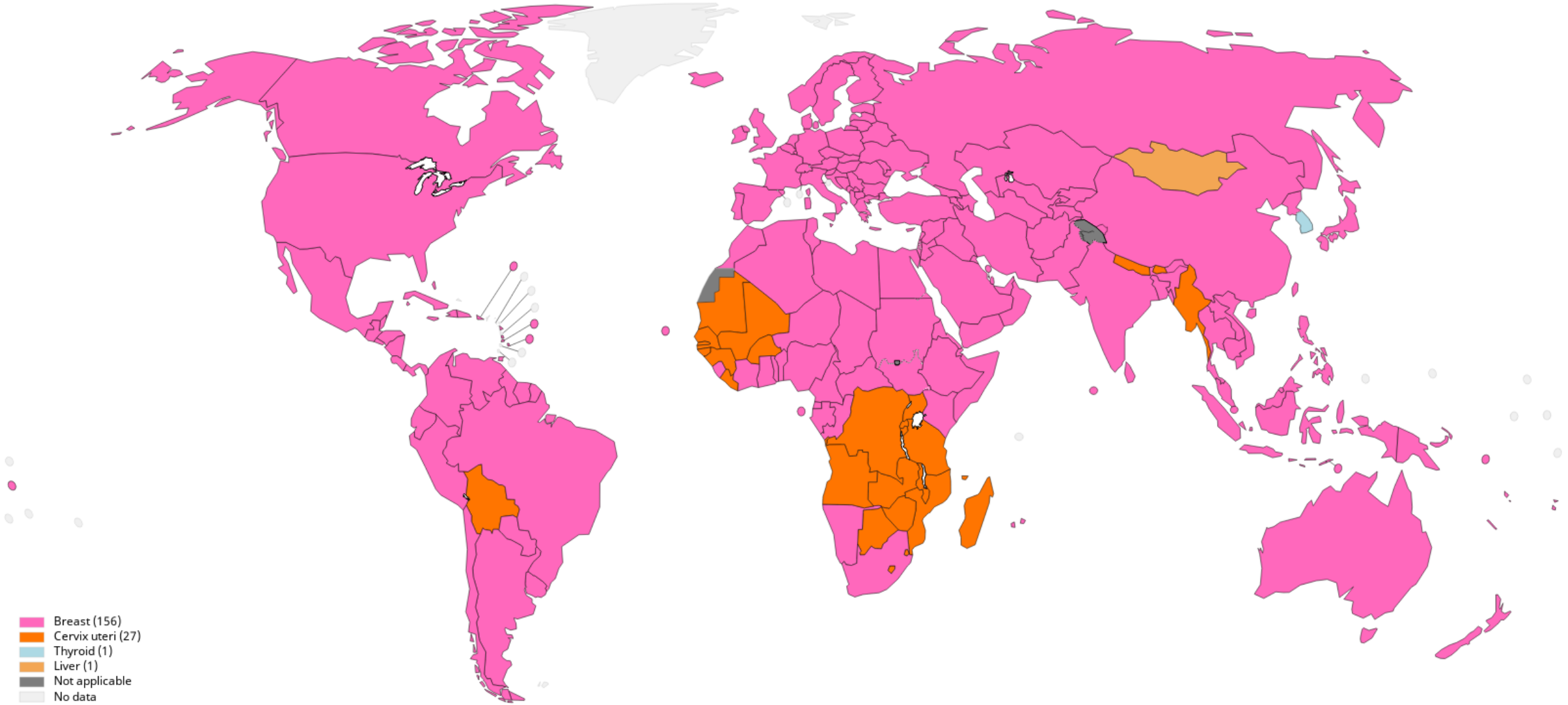
Top cancer per country, estimated age-standardized incidence rates (World) in 2018, females, all ages



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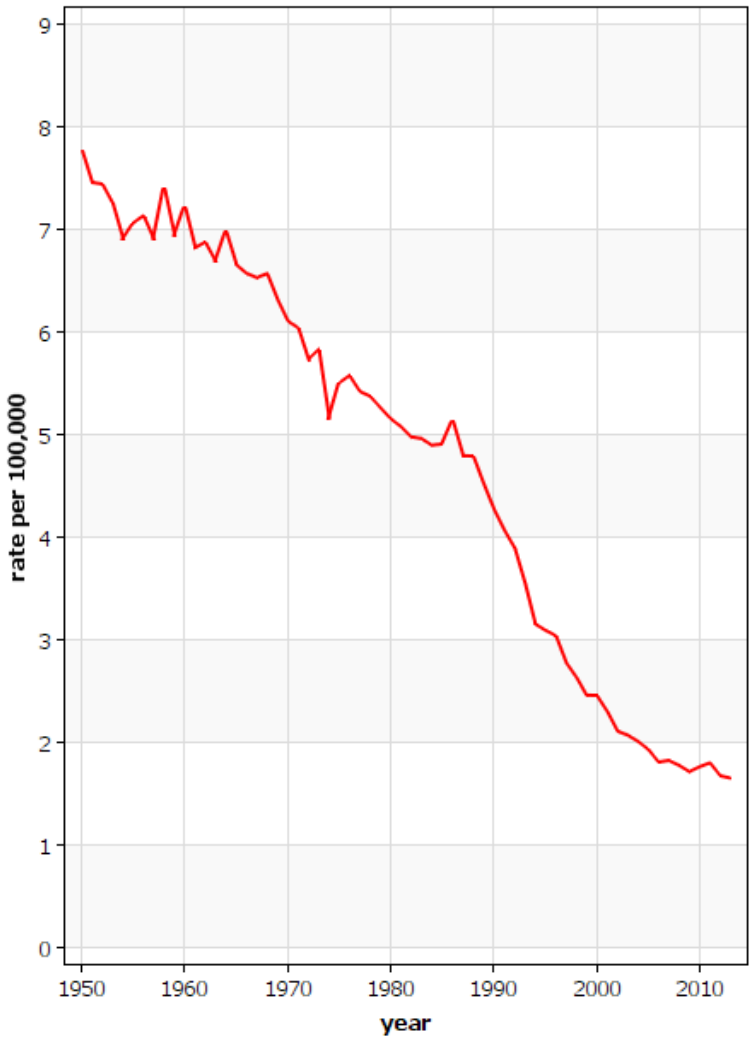
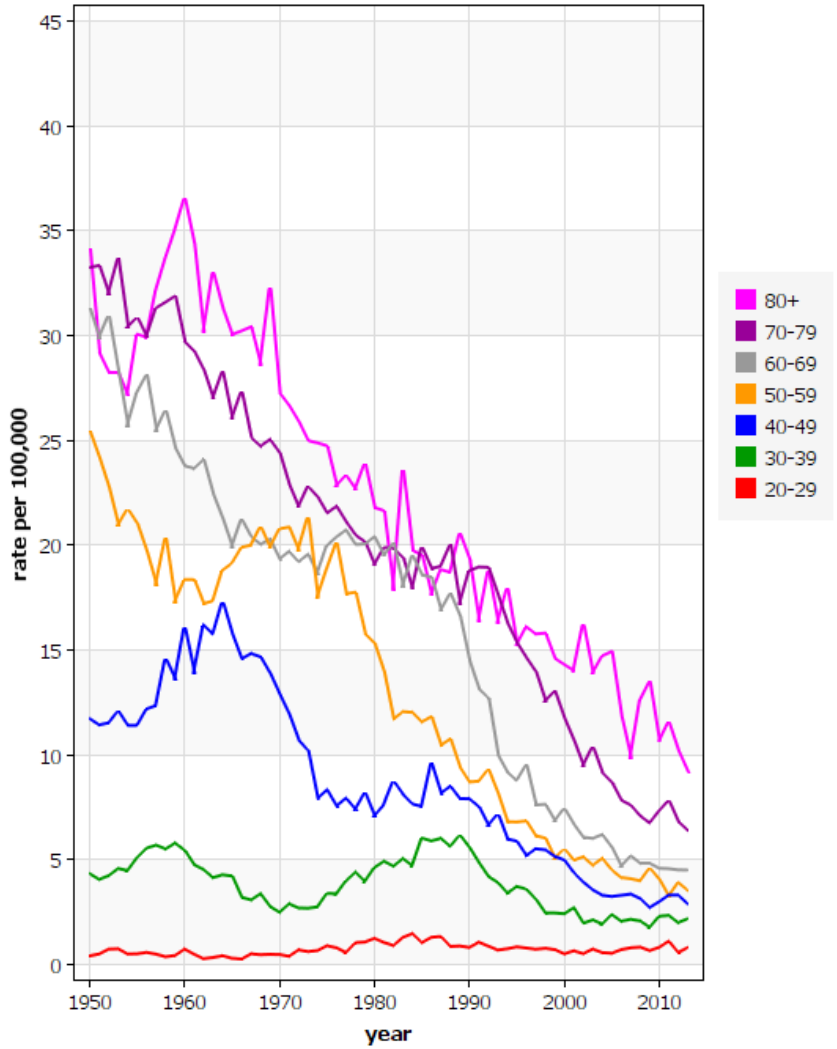
Mortality from Cervical cancer
United Kingdom
Age-standardised rate (World), all ages



International Agency for Research on Cancer
World Health Organization

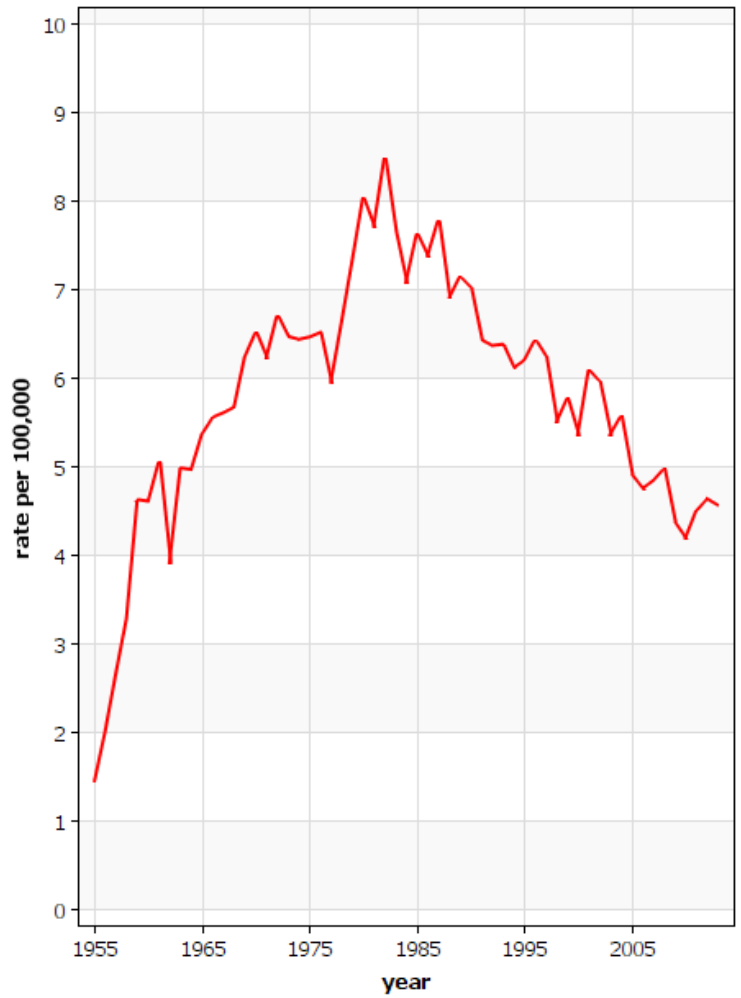
United Kingdom
Mortality from Cervical cancer



International Agency for Research on Cancer (IARC) - 24.6.2019

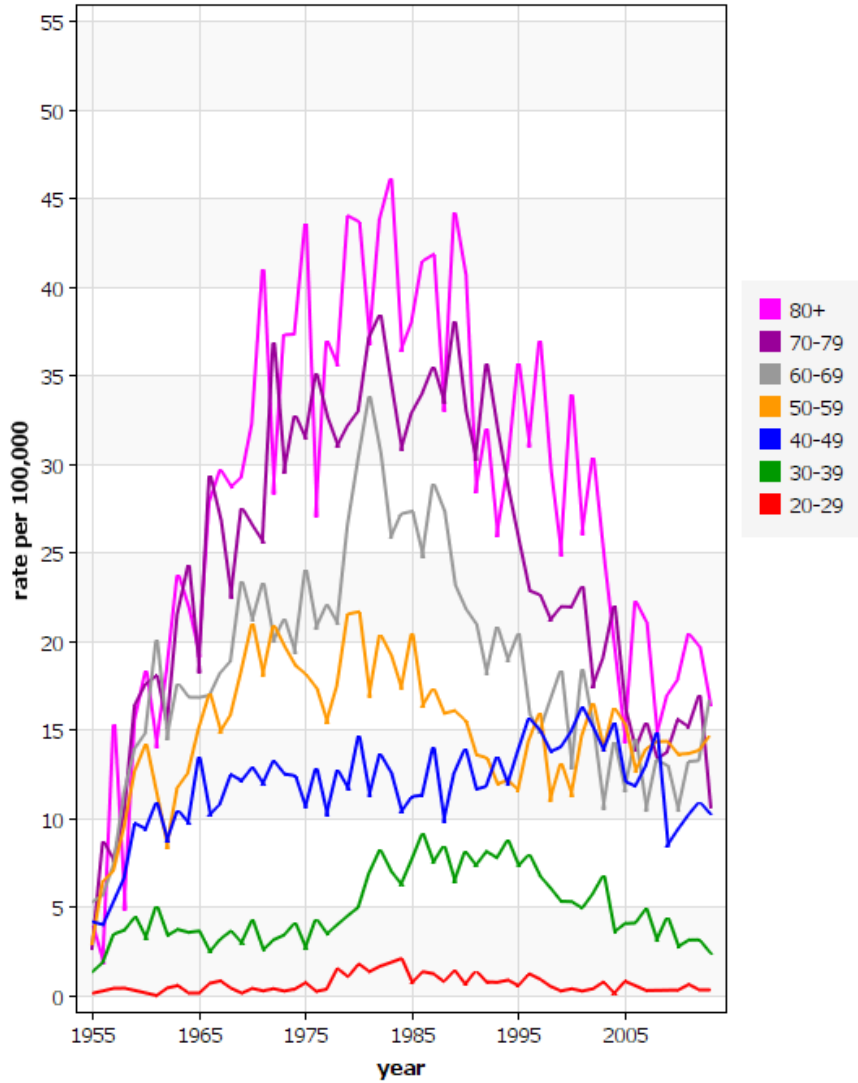
International Agency for Research on Cancer

Mortality from Cervical cancer
Hungary
Age-standardised rate (World), all ages

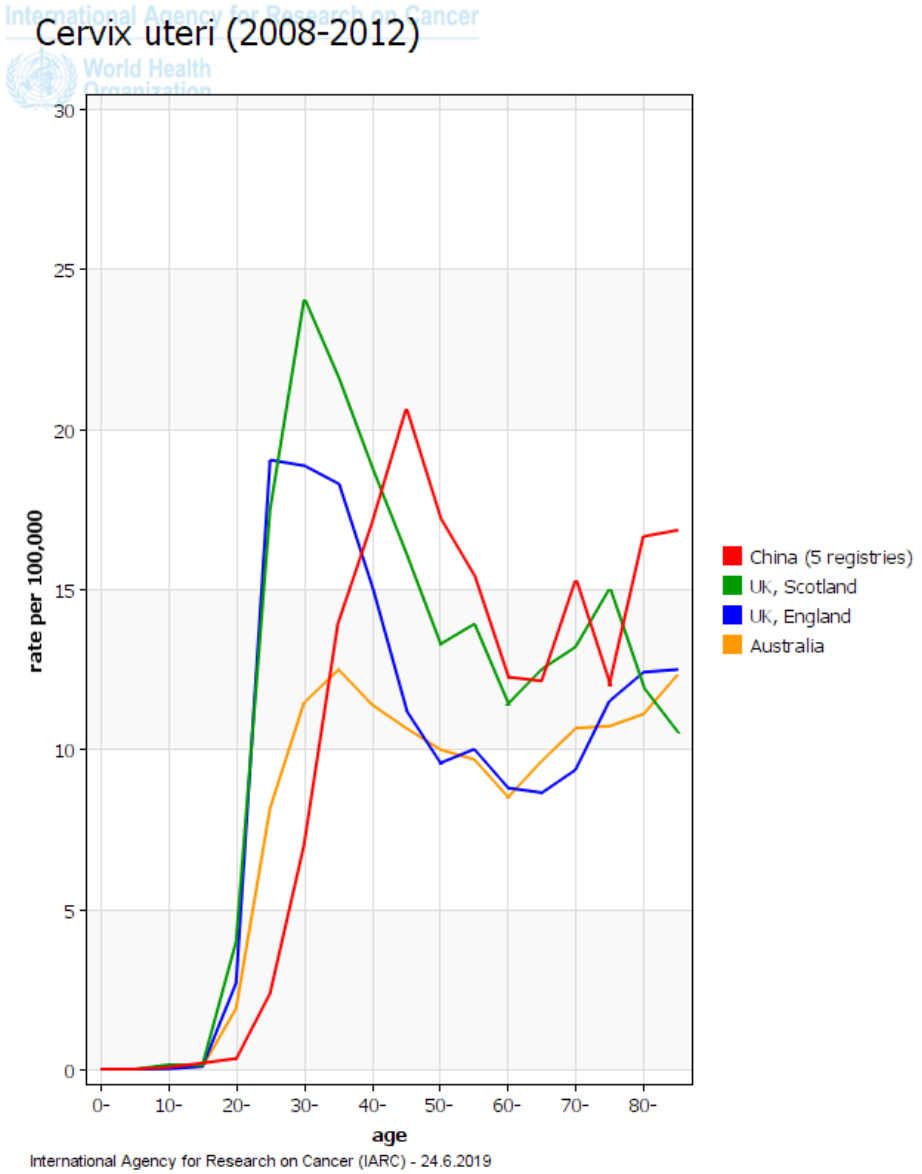


International Agency for Research on Cancer

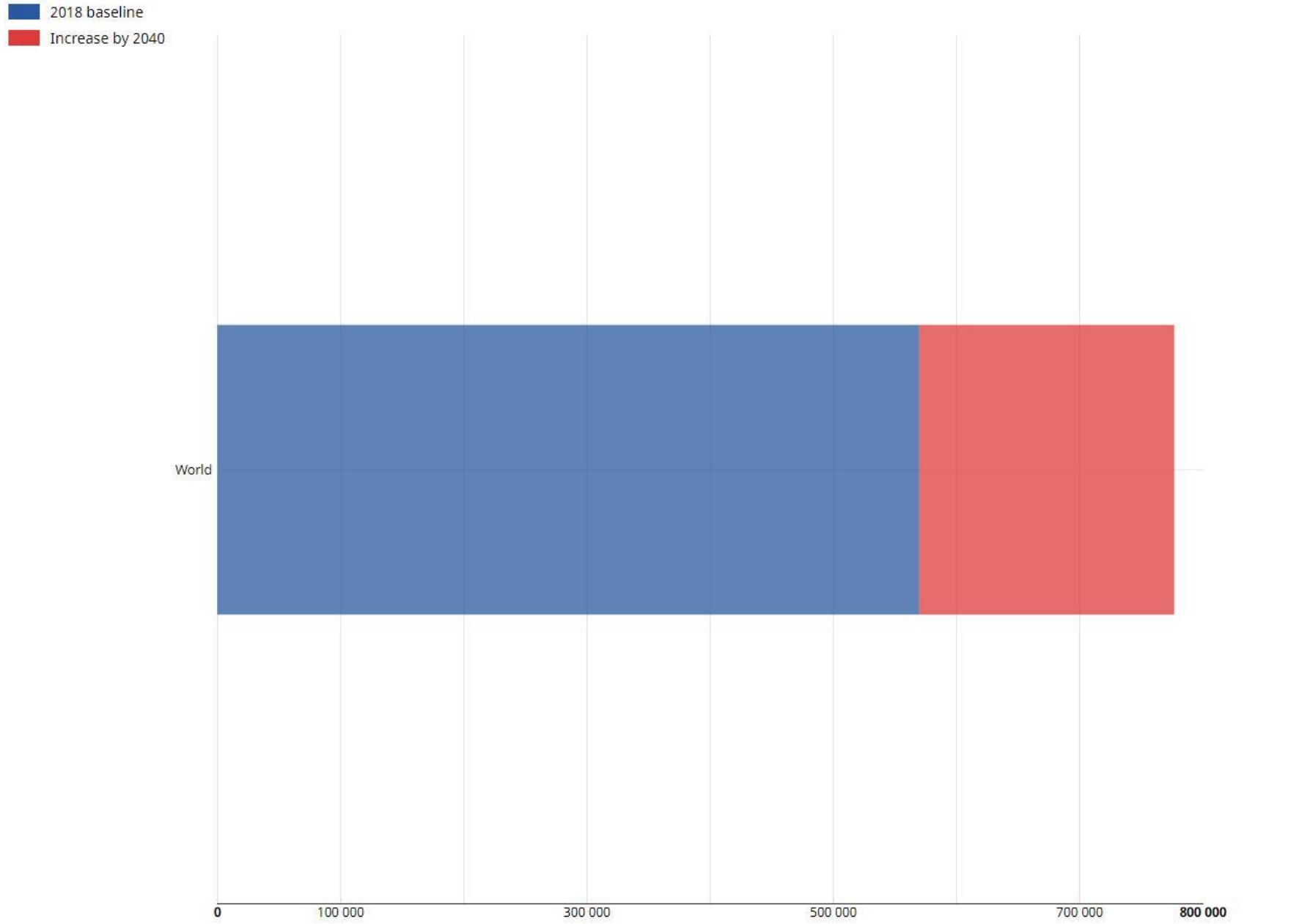
Hungary
Mortality from Cervical cancer



Incidence by Age



Estimated number of incident cases from 2018 to 2040, cervix uteri, females, all ages



Data source:Globocan 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr/)
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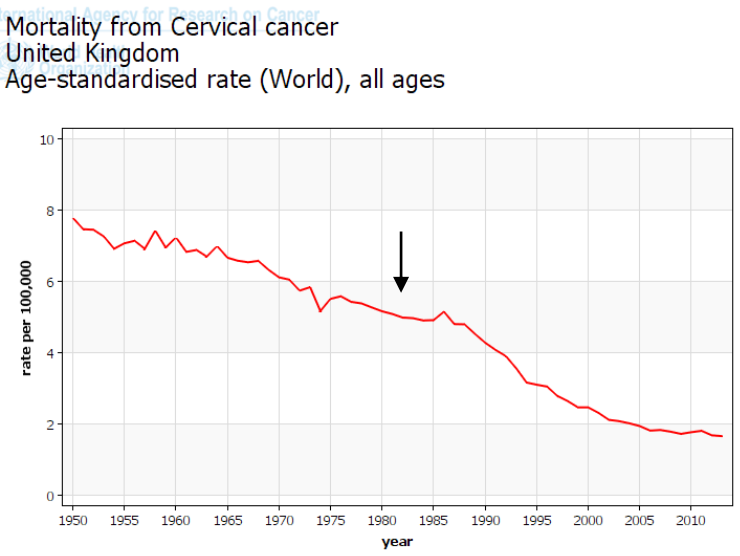
Cervical Screening – The Past

- Introduced in 1988 in the UK
- Cytology only
- Call-recall system
- Tight quality control (technical and interpretive)
- Highly successful



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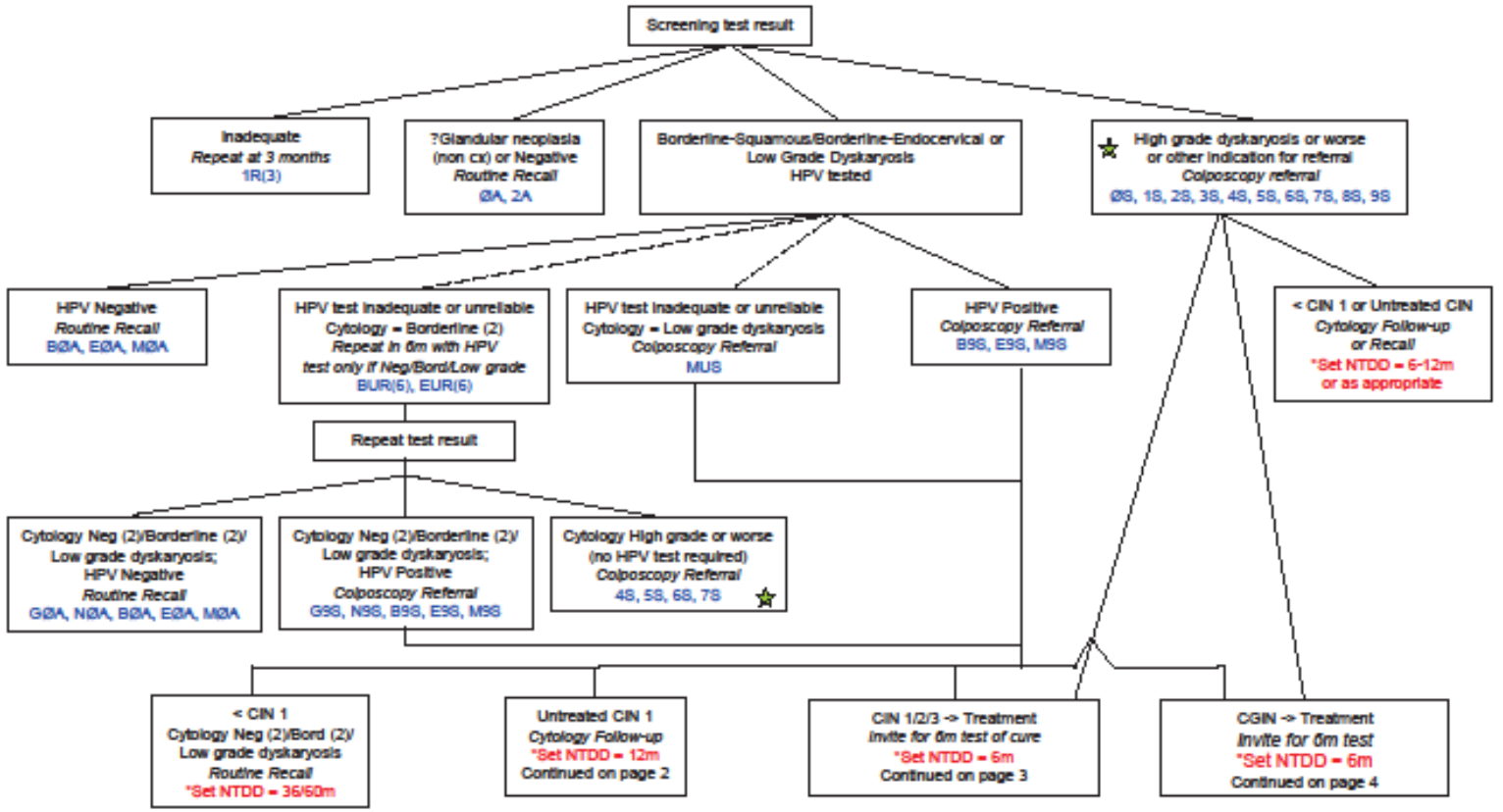
Cervical Screening – The Present

- Cytology is first test
- HPV testing is an adjunct (introduced 2010)
  - Test of cure (after treatment)
  - Triage of low grade abnormalities
  - Specific individual indications
- Effects
  - Test of cure has had an effect on reporting practice
  - HPV testing can be very useful in specific cases e.g. persistent low grade abnormalities

Public Health England

NHS Cancer Screening Programmes

NHS Cervical Screening Programme
Screening Protocol Algorithm for HPV Triage and TOC

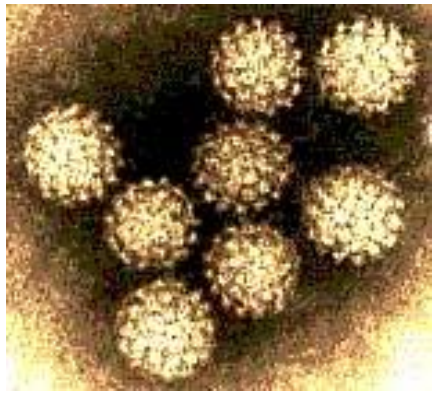


http://www.cancerscreening.nhs.uk/cervical/hpv-triage-test-flowchart-201407.pdf

Cervical Screening – The Future

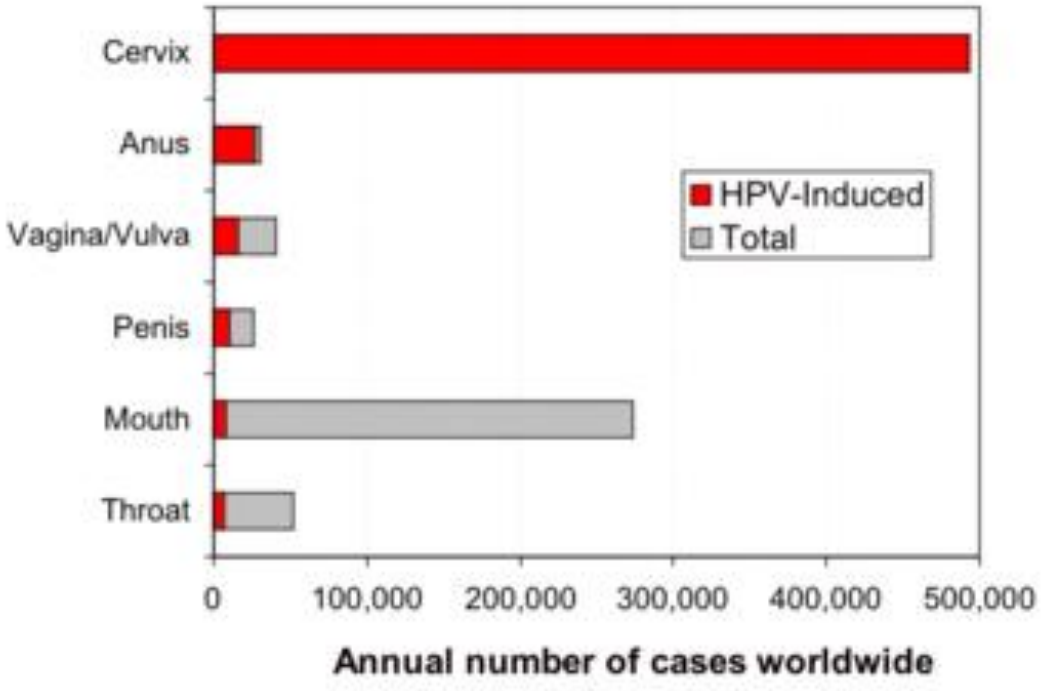
- HPV testing first line
- Reflex cytology
- Consequences
  - Fewer smears = centralization
  - Staffing effects
  - Quality control challenges, particularly cytology/histology correlation
- Vaccination effects

Human Papillomavirus Infection and Anogenital Disease



- HPV infection is present in 99.7% of invasive cervical carcinomas

- Testing for high risk HPVs will therefore have high sensitivity for the detection of disease



Does Presence = Relevant Infection?

- Sensitivity of molecular techniques is a problem
- Non-morphological techniques do not identify origin of sequence
- Relevance depends on application
  - Ubiquitous vs unusual/rare organisms

HPV Testing in Cervical Screening

- Follow-up after treatment
  - 'Test of cure'
- Specific Groups
  - Low grade abnormalities
  - Immunosuppressed patients
- Population screening
  - Adjunct to cytology
  - Replacement for cytology
  - Initial screening modality with reflex cytology

Testing the Test

		Disease	
		Present	Absent
Test	Positive	a	b
	Negative	c	d

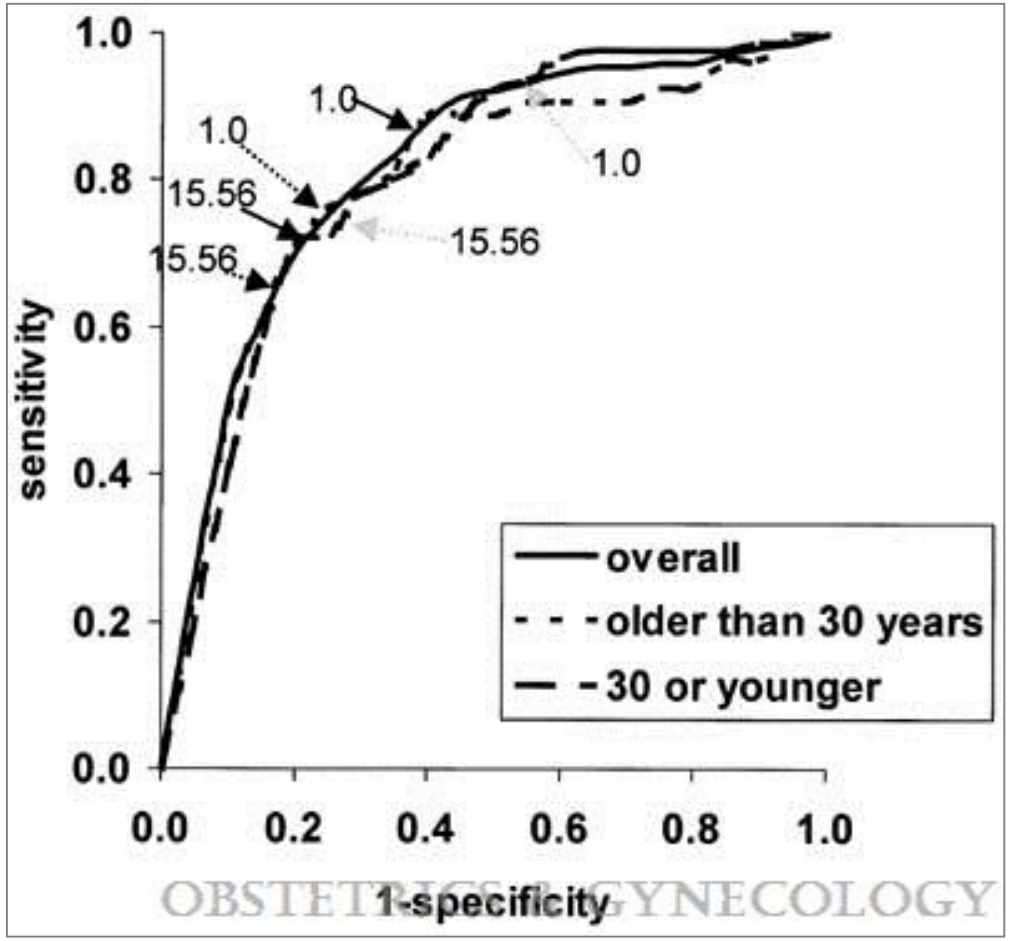
Sensitivity = a / a+c

Specificity = d / b+d

Positive Predictive Value = a / a+b

Negative Predictive Value = d / c+d

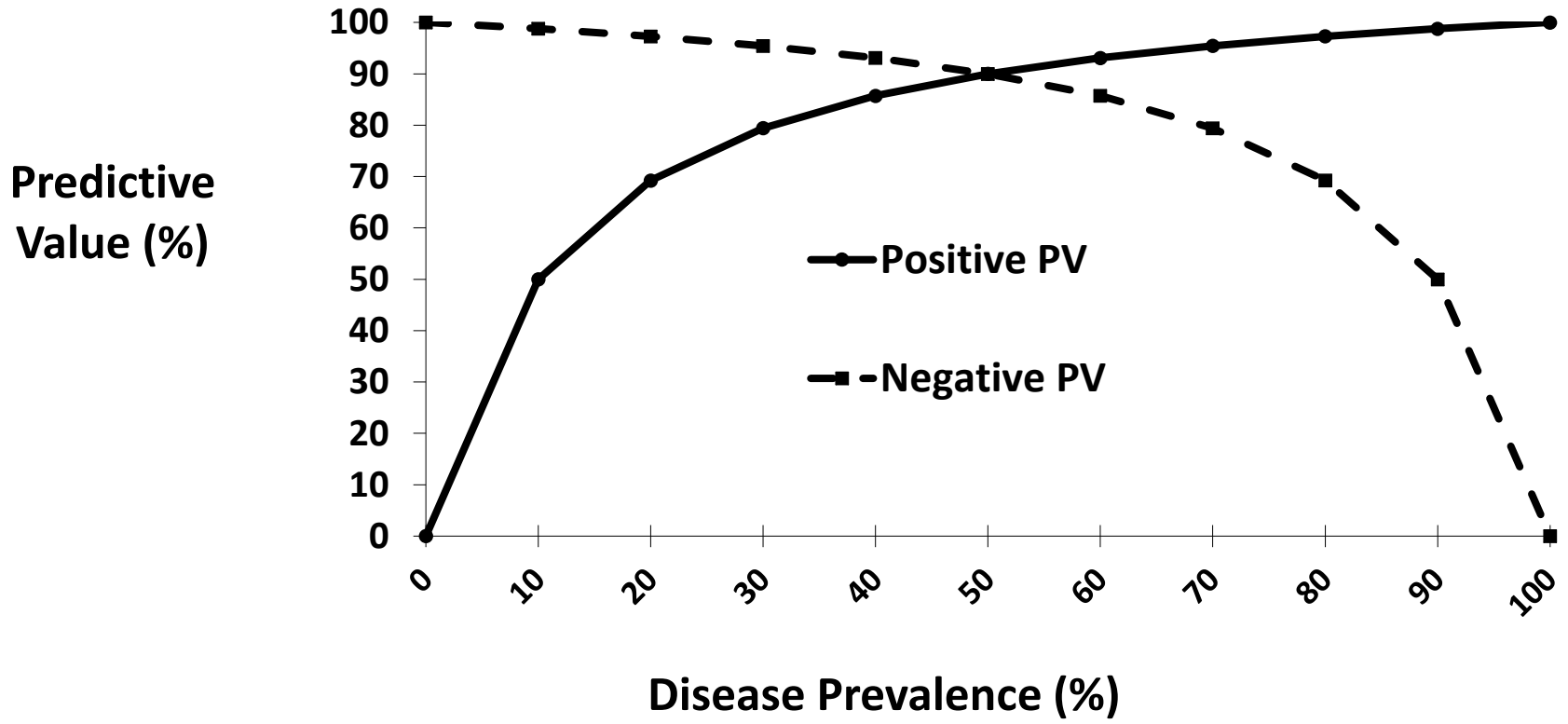
Receiver Operating Characteristic (ROC) Curve Analysis of Hybrid Capture 2



Optimum balance between sensitivity and specificity at '15.56 relative light units' (AUC 0.82)

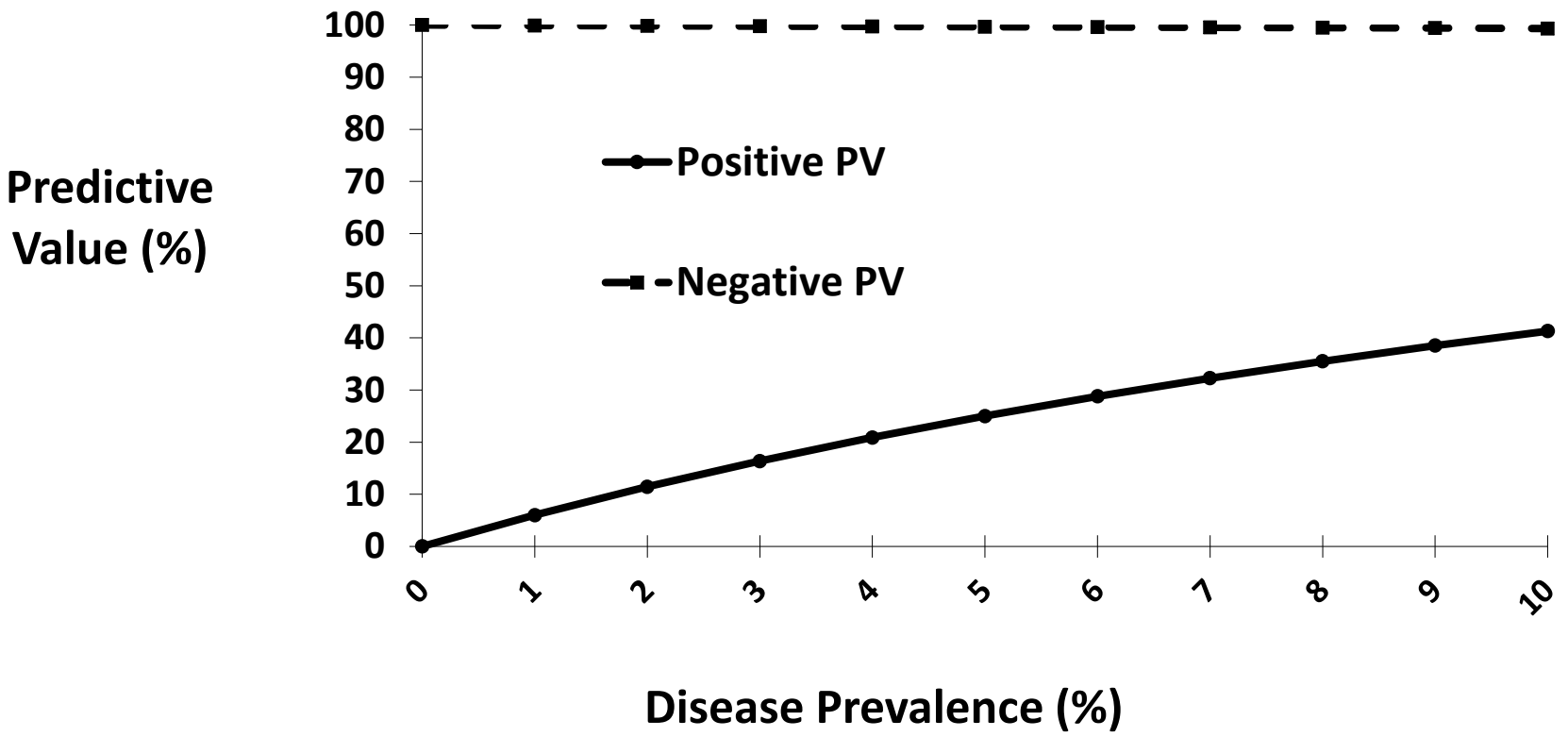
Howard et al. Obstet Gynecol 2002; 100: 972-980

Clinical Prediction



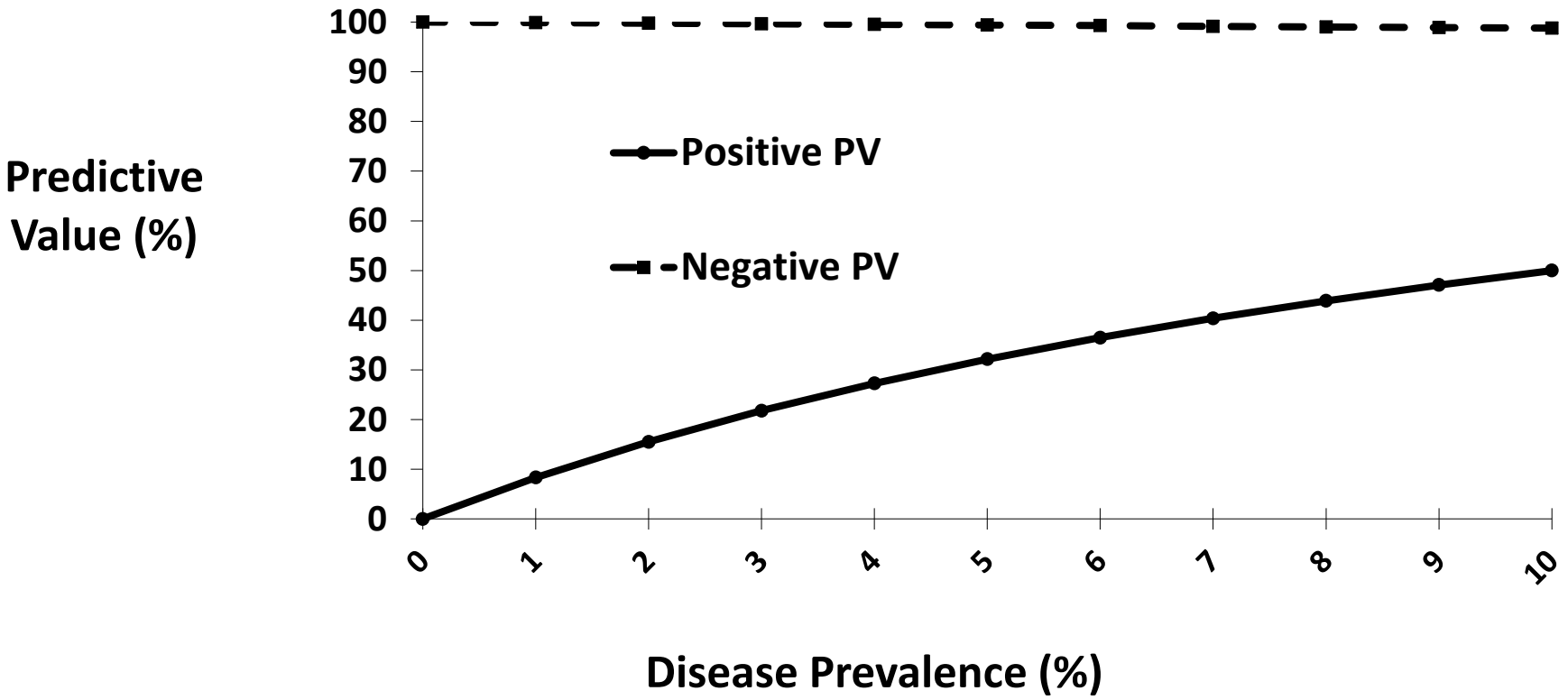
Sensitivity = Specificity = 90%

Clinical Prediction



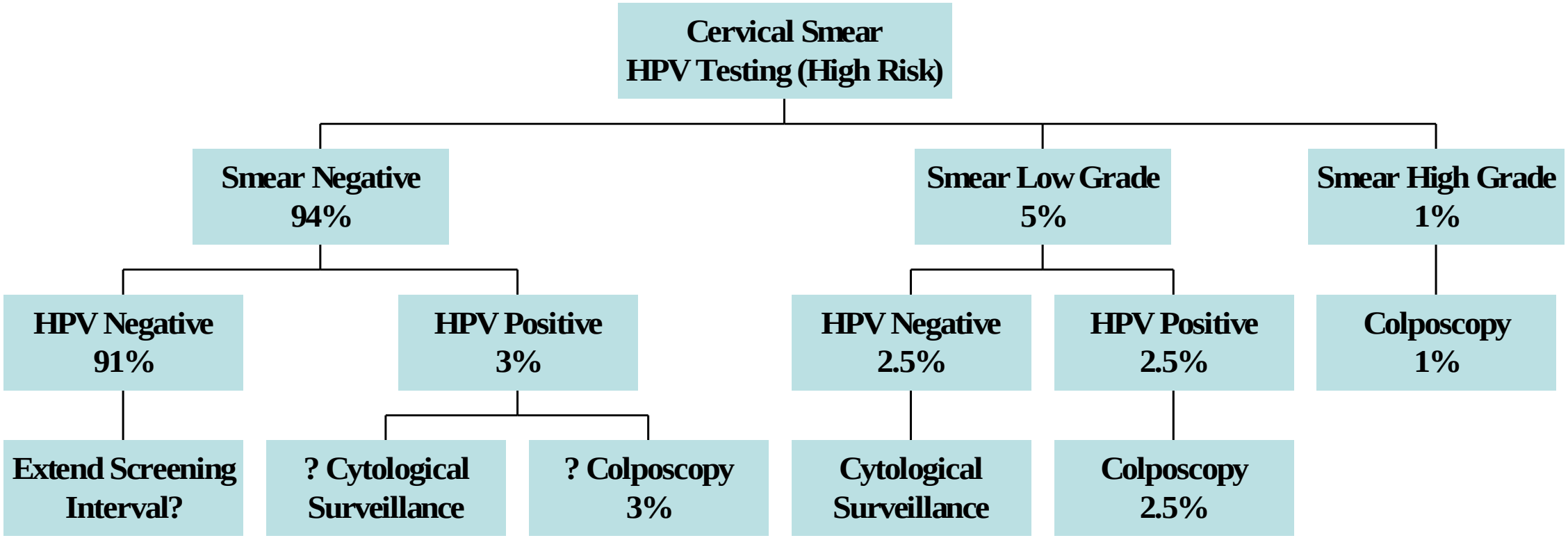
Sensitivity = Specificity = 90%

Clinical Prediction

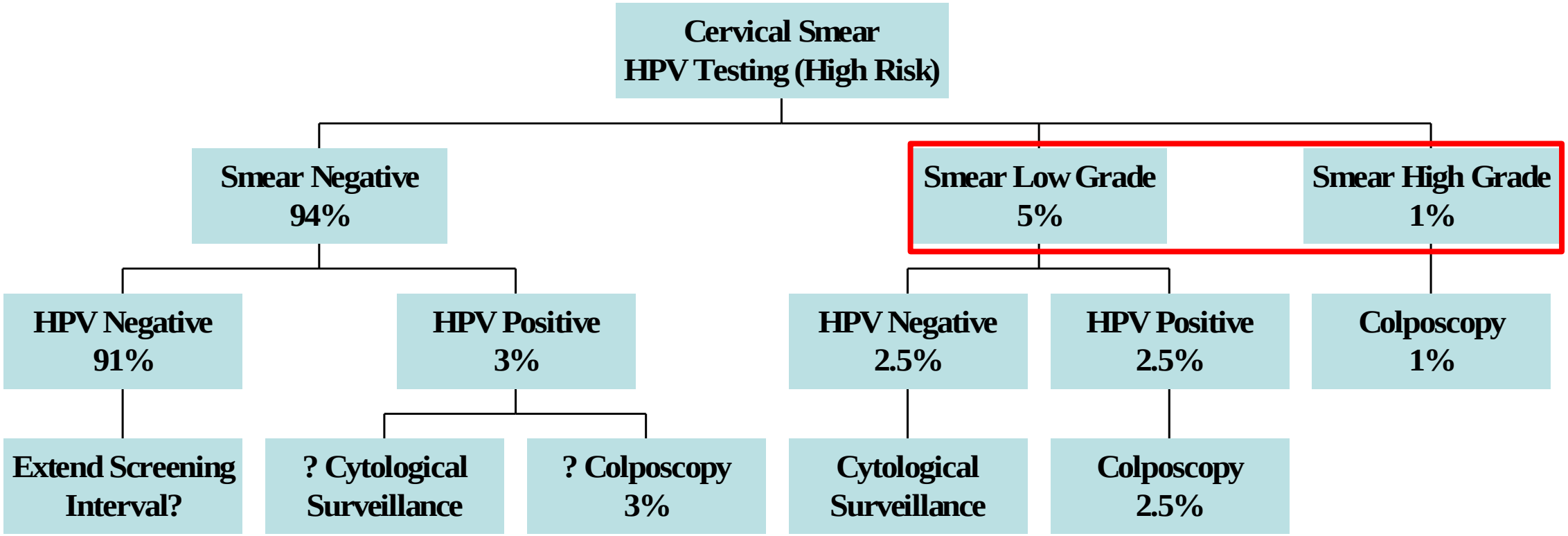


Sensitivity = 95%, Specificity = 85%

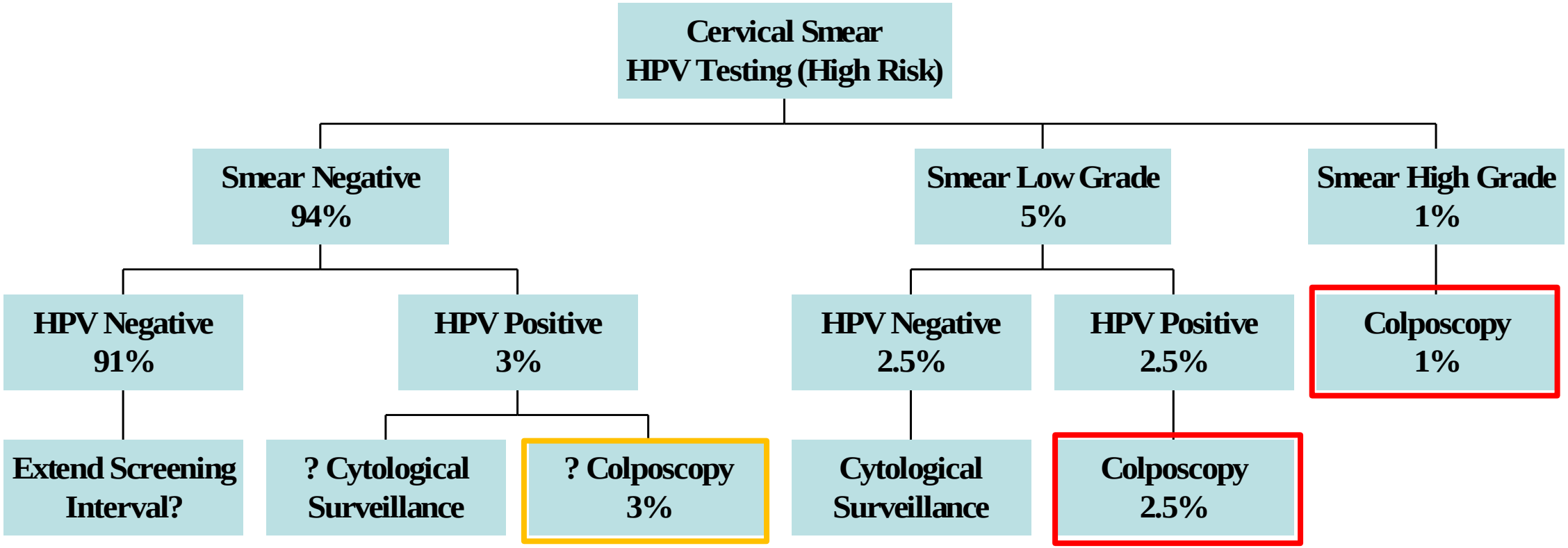
HPV Testing as an Adjunct to Cytology



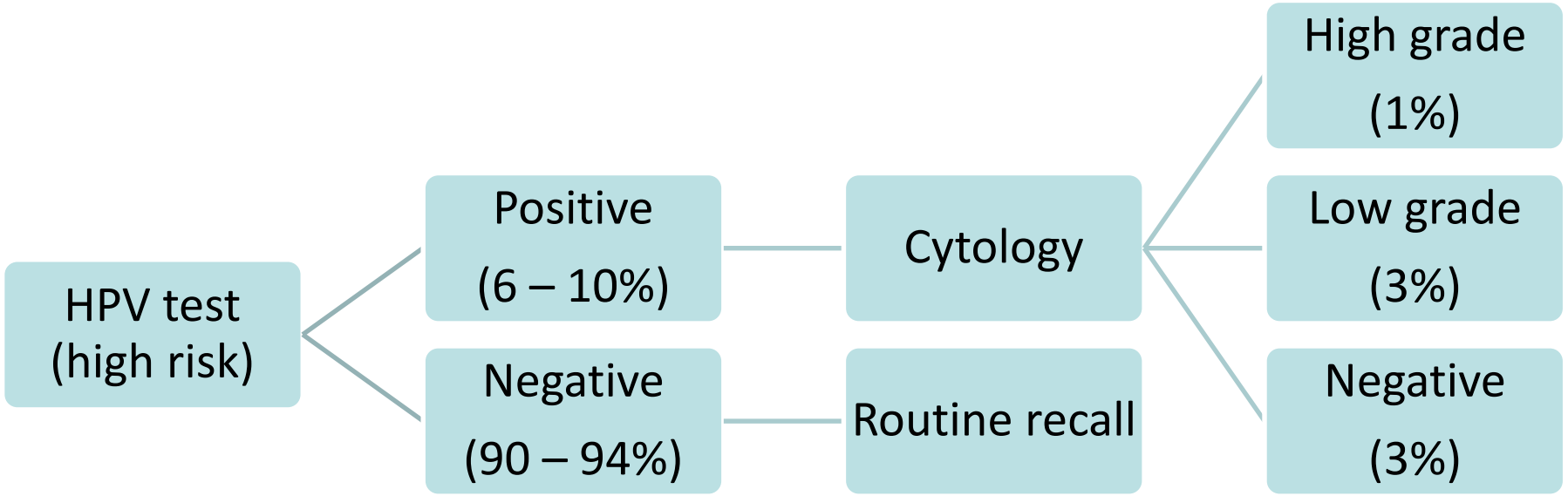
HPV Testing as an Adjunct to Cytology



HPV Testing as an Adjunct to Cytology



Primary HPV Testing



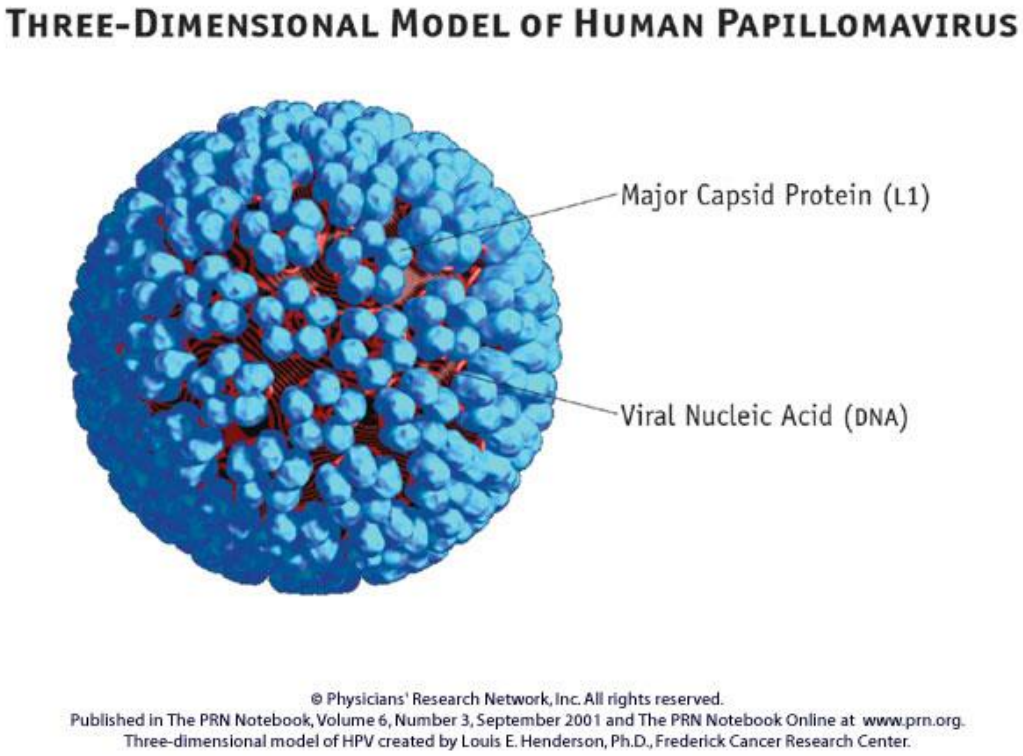
Issues:

- False negatives sent to routine recall
- Who should be referred for colposcopy?
  - High grade – yes
  - Low grade – repeat HPV test?
  - Negative – repeat HPV test?

HPV Testing in Cervical Screening

- Adjunct to cytology
  - Helps with low grade abnormalities
  - Misses HPV positive, smear negative
  - No need for HPV testing if high grade (1%)
- Replacement for cytology
  - Not feasible in view of low positive predictive value
- Initial screening modality with reflex cytology
  - Best compromise
  - Primary screen with high sensitivity but low positive predictive value
  - Reflex cytology provides specificity

HPV Vaccination



- Prophylactic vaccination
  - HPV 16/18 virus-like particles (VLPs)
  - Prevents incident and persistent infection
  - Prevents cytological abnormality

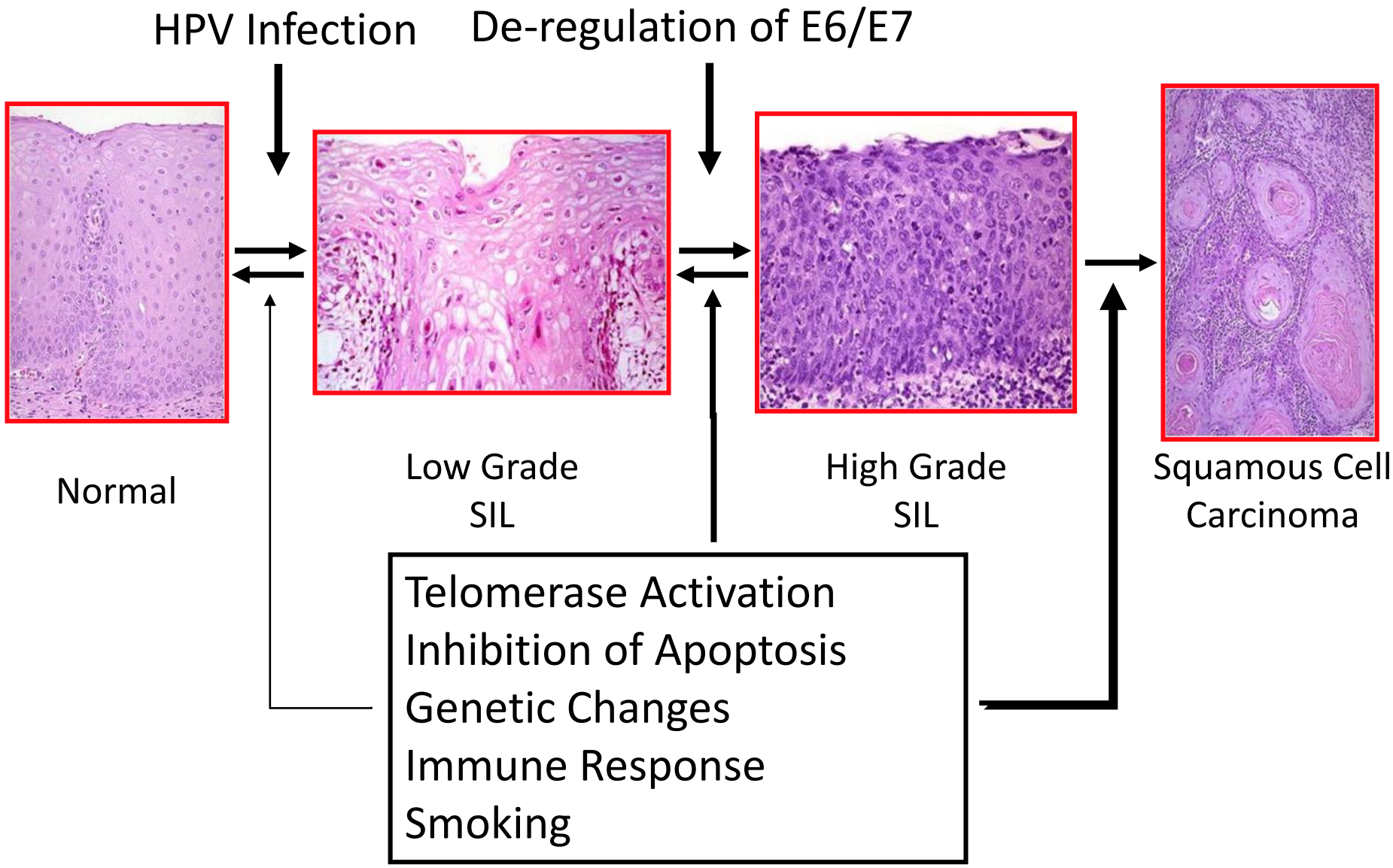
"Vaccines work, but we need more information before widespread immunisation"

Harper D et al *Lancet* 2004; 364: 1757-65

Harper D et al *Lancet* 2006; 367: 1247-55

Stanley M *Br J Cancer* 2007; 96: 1320-3

HPV and Squamous Neoplasia

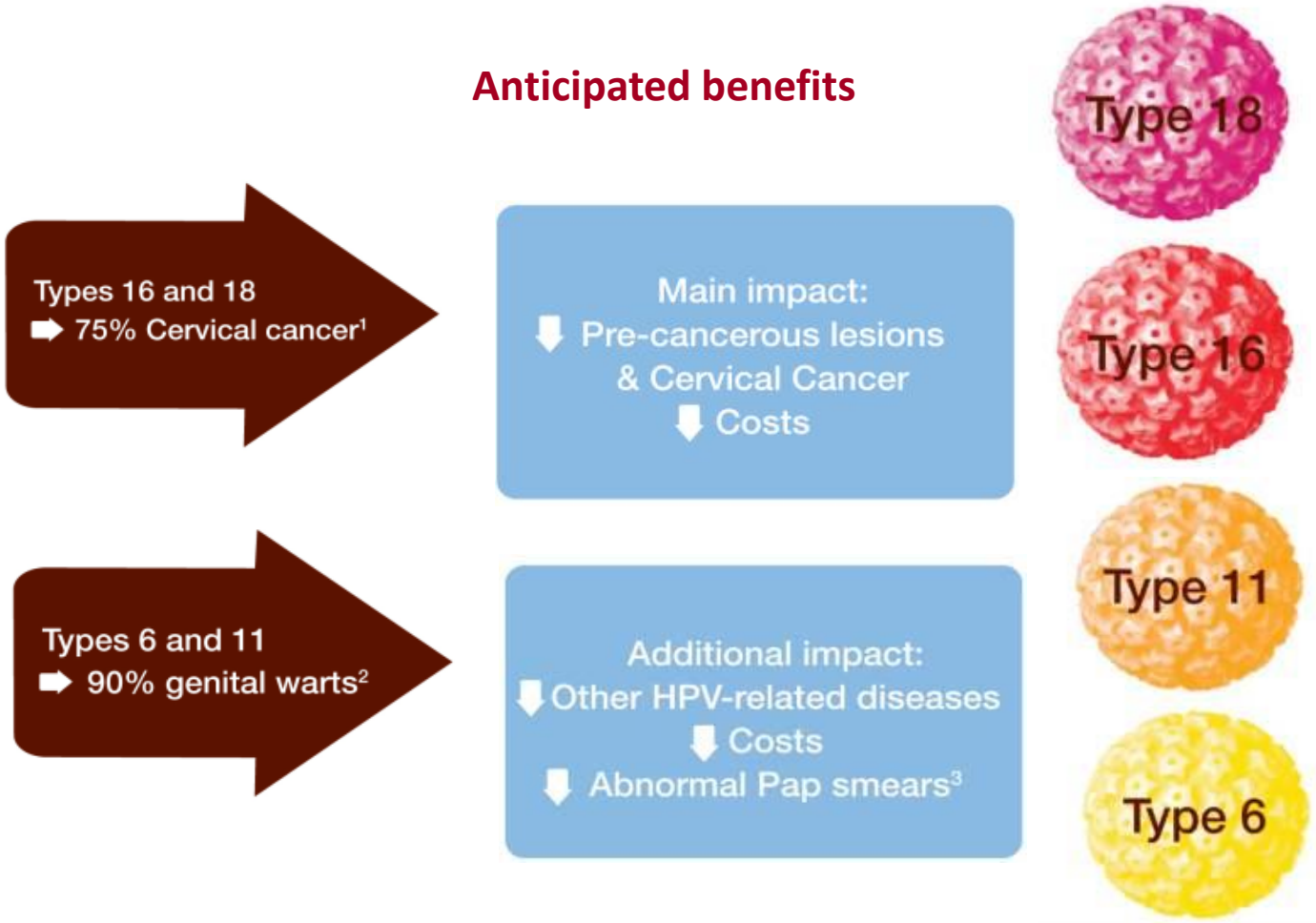


Issues

- Types of HPV vaccination
- Measures of efficacy
- Ideal versus reality
- Outstanding questions

Rationale for Designing a Quadrivalent HPV Vaccine ('Gardasil')

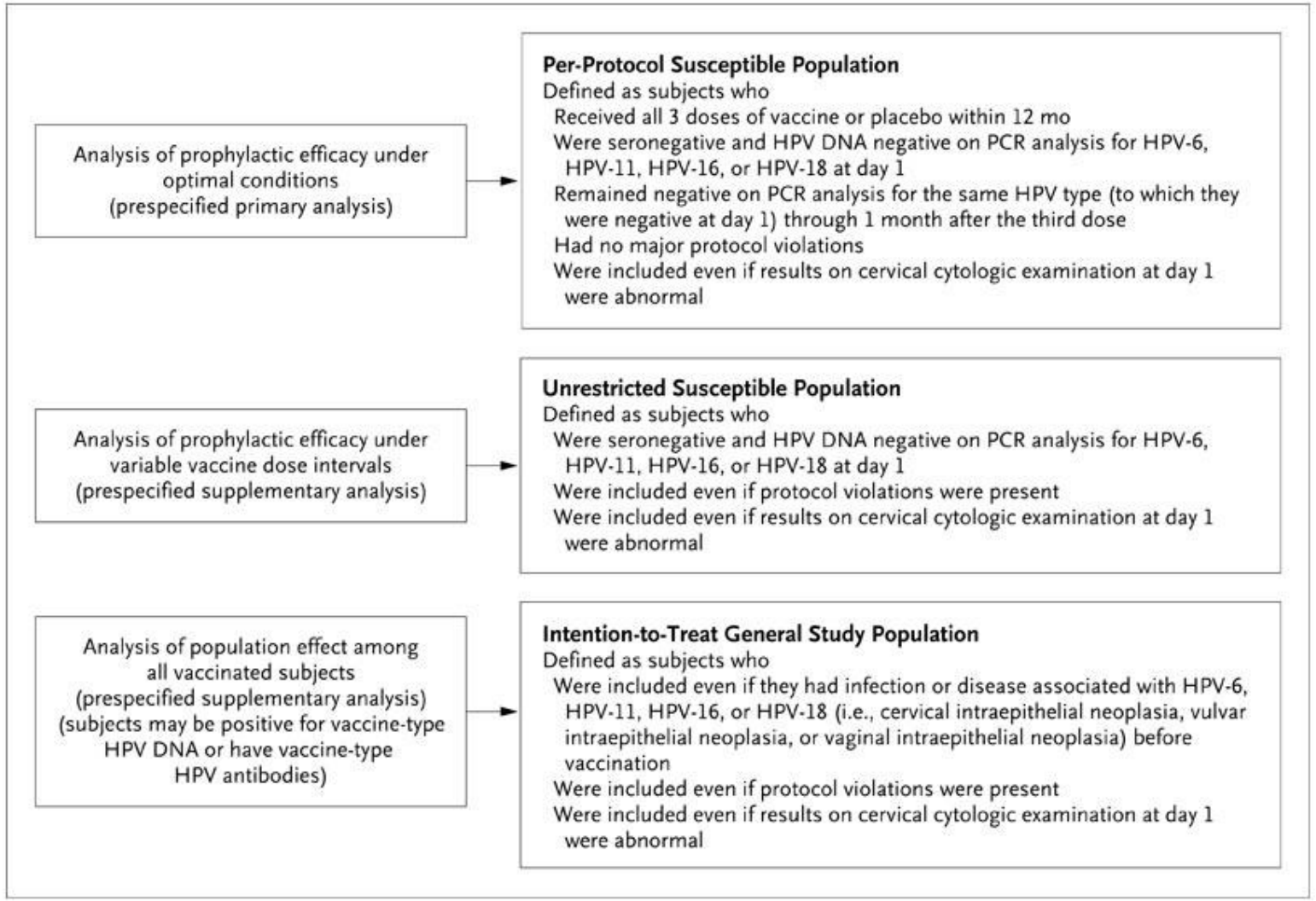
Reason for choice of the human papillomavirus types



Factors Affecting Outcome

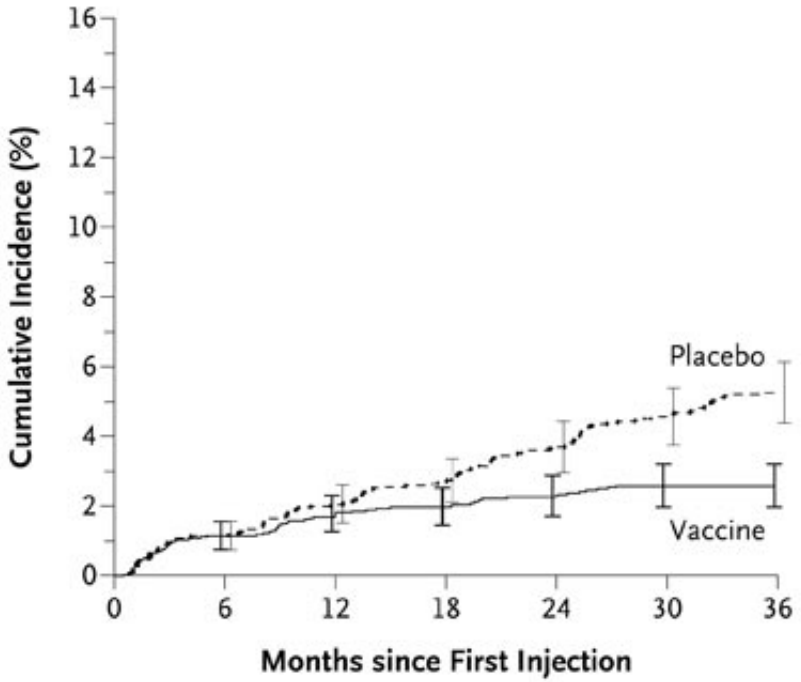
- Vaccine uptake
- Protocol violation
- Other HPV types
- Existing infection with vaccine HPV types
- Vaccine waning

Study Populations



Garland et al. N Engl J Med 2007; 356: 1928-43.

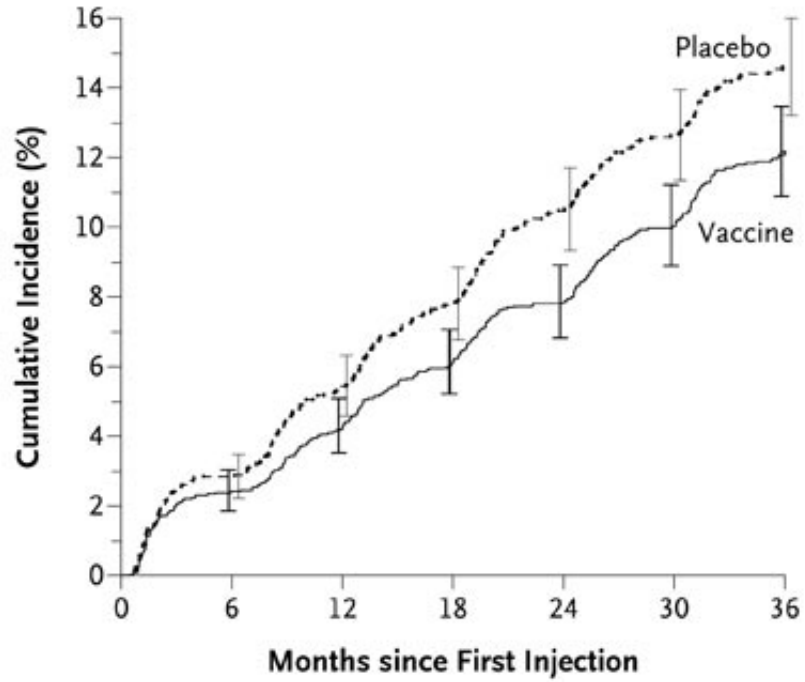
C CIN Grade 1, 2, 3, or Worse Associated with Vaccine-Type HPV



No. at Risk							
Vaccine group	2723	2562	2505	2443	2382	2293	1249
Placebo group	2732	2566	2497	2419	2345	2249	1222

Cumulative No. of Subjects with an End Point							
Vaccine group	0	30	46	51	59	66	66
Placebo group	0	30	53	70	94	115	131

D CIN Grade 1, 2, 3, or Worse, Regardless of Causal HPV Type



No. at Risk							
Vaccine group	2723	2536	2455	2365	2290	2180	1168
Placebo group	2732	2531	2423	2325	2221	2115	1129

Cumulative No. of Subjects with an End Point							
Vaccine group	0	63	111	158	201	255	304
Placebo group	0	74	141	201	269	321	367

Times to End-Point Events in the Intention-to-Treat Population
Garland et al. N Engl J Med 2007; 356: 1928-43.

Cervix - Combined Analysis of 4 RCTs

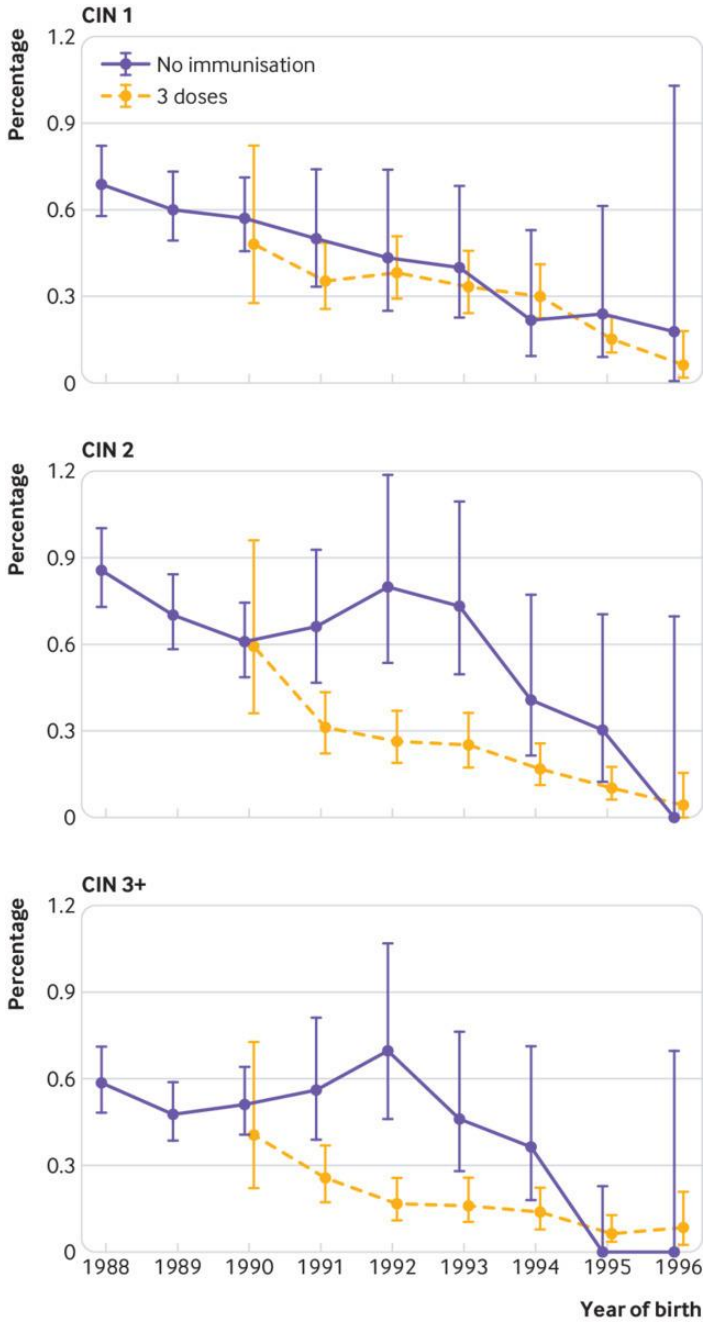
HPV16/18-related CIN2/3 or AIS

	Vaccine (N=10291)			Placebo (N=10292)			Efficacy
	N	Cases	Rate	N	Cases	Rate	
Per-protocol susceptible population	8579	1	<0.1	8550	85	0.4	99%
Unrestricted susceptible population	9729	3	<0.1	9737	77	0.3	99%
Intention to treat population	10291	142	0.5	10292	255	0.9	44%

Ault KA. Lancet 2007; 369: 1861-8 - ‘Gardasil’

HPV Vaccination

- HPV vaccination works, particularly in susceptible populations
- Effects are modified by:
  - Pre-existing infection
  - Non-vaccine HPV types
  - Protocol violation
- Duration of protection not clear
- Effects on invasive disease are assumed, not proven



Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland

- Retrospective study of women born 1988 – 1996 and who had smear at age 20
- Routine vaccination of girls aged 12-13 years with the bivalent HPV vaccine in Scotland has led to a dramatic reduction in preinvasive cervical disease.
- Evidence of clinically relevant herd protection is apparent in unvaccinated women

Palmer et al Br Med J 2019; 365: l1161

Lancet Paper This Week

- Systematic review and meta-analysis
- Data from 60 million individuals and up to 8 years of post-vaccination follow-up
- Compelling evidence of the substantial impact of HPV vaccination programmes on HPV infections and CIN2+ among girls and women, and on anogenital warts diagnoses among girls, women, boys, and men.
- Programmes with multi-cohort vaccination and high vaccination coverage had a greater direct impact and herd effects.

Drolet et al Lancet 2019; https://doi.org/10.1016/S0140-6736(19)30298-3

Conclusions

- Persistent ‘high-risk’ HPV infection is strongly associated with cervical neoplasia
- HPV testing will take over from cytology as the primary screening modality
- HPV vaccination is likely to change things!
- But vaccination is unlikely to be the whole answer

